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Single- and Multiple-Dose Pharmacokinetics of Pipemidic Acid in Normal Human Volunteers

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The pharmacokinetic profile of pipemidic acid was studied in two groups of young healthy volunteers by using a new, sensitive, high-pressure liquid chromatography procedure for quantitation of pipemidic acid in biological fluids. After oral or intravenous administration, the disposition of pipemidic acid may be described as a one- or a two-compartment open model, respectively. Oral bioavailability was 93.1 ± 11% (mean ± standard error). After administration of a 100-mg tablet, 13.4 ± 2.7% was bound to serum proteins at the time of peak drug concentration in serum. Excretion of pipemidic acid in saliva was negligible, the saliva/serum ratio being about 0.32. At steady state after the twice-daily administration of a 500-mg tablet, which is a recommended dosage regimen, a peak drug concentration in serum of 4.3 ± 0.5 μg/ml was attained in 1.2 ± 0.1 h. The apparent volume of distribution was 1.9 ± 0.2 liters/kg, and the elimination half-life was 3.4 ± 0.2 h. The renal clearance was 4.3 ± 0.7 ml/min per kg, and the total clearance was 6.3 ± 0.5 ml/min per kg. Despite a considerable water load, the minimum concentration in urine at the end of a dosing interval averaged 100 μg/ml, which widely exceeds the known MIC of pipemidic acid against bacteria commonly causing urinary tract infections.

Although pipemidic acid (PPA), a structural relative of nalidixic acid (NA), has been used in the treatment of urinary tract infections for more than 8 years, there have been few studies of its pharmacokinetics. The studies performed on patients with impaired renal function (8, 12, 12a, 18) are more comprehensive than those performed on healthy subjects (2, 3, 13, 16). The bioavailability of PPA has been determined only on the basis of its excretion in urine and except for certain urinary data (3), there are no studies of PPA kinetics at steady state. Also, there are no studies of PPA excretion in saliva. The present work was undertaken to extend the knowledge of the pharmacokinetics of PPA in healthy volunteers.

(A preliminary account of a minor part of this work was presented at the Joint Meeting of the Scandinavian and German Pharmacological Societies [E. Klinge, P. T. Männistö, S. Nykänen, U. Lamminsivu, and H. Jousimies-Somer, 1980. Naunyn-Schmiedeberg's Arch. Pharmacol. 313(Suppl):R55, abstr. no. 217].)

MATERIALS AND METHODS

General design. The study consisted of two separate experiments. In experiment 1, PPA systemic availability, binding to plasma proteins, and concentration in saliva were measured by giving 100 mg of PPA as a single oral dose or as an intravenous infusion to six healthy volunteers. In experiment 2, the levels of PPA in serum and the excretion of PPA in urine were determined in 10 healthy volunteers after a single oral dose of 500 mg and at steady state after twice-daily administration of the same dose for 6 days. The latter is the dosage regimen of PPA recommended for the treatment of urinary tract infections. All of the subjects gave informed consent.

Experiment 1. In a cross-over design experiment, one female volunteer (23 years old; 68 kg) and five male volunteers, (23 to 26 years old; mean weight, 68 kg) received 100 mg of PPA as a tablet (lot no. 1/81; Orion Pharmaceutical Co.) or as an infusion via a cubital vein. For the latter procedure, PPA methane sulfonate (lot no. 2/81; Orion Pharmaceutical Co.) was dissolved in 500 ml of 0.9% NaCl which was infused by using an infusion pump at a constant rate during 60 min. The treatments were performed at weekly intervals starting at 8:00 a.m. after an overnight fast. After the oral dose, blood samples were withdrawn at 0.5, 1, 1.5, 2, 3, 4, 5, 6, and 8 h. Additional samples were withdrawn at 5, 10 and 15 min after the intravenous dose. Urine was collected at 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, and 12 to 24 h after dosage. Saliva was collected at 1, 2, 4, and 8 h by having the volunteers spit into test tubes for 1 min after they chewed parafilm.

Serum, saliva, and urine samples were stored at −20°C until they were analyzed. Protein-free fractions of PPA in serum were prepared by ultrafiltration. Samples containing 14 to 16 ml were centrifuged (450 × *g*, 60 to 90 min) in dialysis tubing hanging in a capped centrifuge tube at +20°C.

Experiment 2. Seven female volunteers (22 to 28 years old; mean weight, 58 kg) and three male volunteers (26 to 30 years old; mean weight, 70 kg) participated in experiment 2. For the first part of this experiment, the volunteers drank 400 ml of water at 7:00 a.m. after a night of fasting. At 8:00 a.m., they ingested a 500-mg tablet of PPA (Utivec, lot no. 6/79; Orion Pharmaceutical Co.) with 200 ml of water. They then drank 200 ml of water hourly until noon and 100 ml of water hourly until 4:00 p.m. Eating was not permitted until 10:00 a.m. Blood samples were withdrawn at 0.5, 0.75, 1, 1.5, 2, 3, 4, 5, 6, 7, 8, and 12 h. Urine was collected at 0 to 2, 2 to 4, 4 to 6, 6 to 8, 8 to 12, 12 to 16, 16 to 24, 24 to 48, and 48 to 72 h.

In the second part of this experiment, which started 3 days after the first part, the same subjects ingested two 500-mg tablets at 8:00 a.m. on the first day and one such tablet every 12 h until 8:00 a.m. of day 6. Sampling was performed on days 5 and 6, during which the water load and the dietary restrictions were the same as in the first part of this experiment. On day 5, blood samples were withdrawn just before and 1, 2, 3, and 8 h after ingestion of the morning

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tablet. On day 6, blood samples were again withdrawn just before ingestion of the morning tablet, and thereafter 12 samples were withdrawn as in the first part. On day 5, urine was collected at 0 to 2, 2 to 4, 4 to 6, and 6 to 8 h. On day 6 and on the two days following, nine successive fractions were collected as in the first part.

Analytical techniques. Concentrations of PPA in serum, ultrafiltrate, saliva, and urine were determined by high-pressure liquid chromatography as follows. Serum proteins were precipitated by adding 3.0 ml of 0.5 M perchloric acid to 1.0 ml of sample. After 10 min of standing and centrifugation (2,500 × *g*, 10 min), 2.0 ml of the supernatant was neutralized with 1.0 ml of 0.5 M sodium phosphate and washed with 5.0 ml of chloroform. A 0.5-ml volume of ultrafiltrate and a 0.5-ml volume of saliva were acidified with 1.5 ml and 0.15 ml of 0.5 M perchloric acid, respectively. After 10 min of standing and centrifugation, (2,500 × *g*, 10 min), 1.0 and 0.5 ml of the supernatants were neutralized with 0.5 ml of 0.5 M sodium phosphate and washed with 2.5 ml of chloroform. A 100-μl volume of urine was diluted with 10 ml of 35% (vol/vol) methanol in 0.07 M phosphate buffer (pH 8.2).

Fractions (20 to 40 μl) were analyzed by use of a high-pressure liquid chromatograph consisting of a Waters model 6000 A solvent delivery system, a Wisp 710B automatic injector, and a μBondapak column (C18; 10 μm, 30 cm by 3.9 mm). A precolumn packed with LiChroprep RP2 (E. Merck AG, Darmstadt, Germany) was installed between the pump and the column. Samples were eluted at a rate of 1.5 ml/min (2,300 lb/in^2) with 35% (vol/vol) methanol in 0.07 M phosphate buffer (pH 8.2).

PPA was quantitated by comparing peak heights of PPA in samples with the calibration curves constructed by spiking the control serum, ultrafiltrate, saliva, and urine samples with PPA. Calibration curves were linear within the following ranges: 0.08 to 2.5 μg/ml in serum, 0.05 to 0.62 μg/ml in ultrafiltrate, 0.02 to 0.62 μg/ml in saliva, and 3 to 500 μg/ml in urine. Day-to-day precision determinations were as follows: at 1 μg/ml of serum, 3% (coefficient of variation) (n = 16); at 0.6 μg/ml of ultrafiltrate, 6% (n = 8); at 0.1 μg/ml of saliva, 3% (n = 9); and at 250 μg/ml of urine, 2% (n = 14). Recoveries in the ranges used were 72 ± 3% (mean ± standard deviation; n = 16) in serum, 96 ± 4% (n = 6) in ultrafiltrate, 98 ± 6% (n = 5) in saliva, and 102 ± 2% (n = 14) in urine. The lower recovery in serum was due to precipitation of the proteins with perchloric acid, but as indicated above, the day-to-day precision was good.

In experiment 2, the concentrations of PPA in urine were also determined microbiologically at the Finnish National Public Health Institute by the agar well-diffusion technique with *Escherichia coli* Kp as the indicator organism (17).

Pharmacokinetic calculations. The drug concentrations in serum measured after the 100-mg intravenous infusion and those measured after the 100-mg oral dose were subjected to computer analysis by using the program AUTOAN (15), followed by the nonlinear iterative least-squares regression program NONLIN (11). The areas under the concentration-time curves (AUCs) were calculated by the trapezoidal rule and extrapolated to infinity ($AUC_{0-\infty}$) by dividing the last data point by the elimination rate constant. Total body clearance (CL_{tot}) was calculated as follows: $CL_{tot} = F \cdot \text{dose/AUC}$, where F is the absolute oral bioavailability. The volume of distribution (V) was calculated by the equation $V = \text{dose/AUC} \cdot k_{el}$ (k_{el} is the elimination rate constant) or β in case of a one- or a two-compartment open model, i.e., after oral and intravenous administration, respectively. The renal clearance (CL_R) was calculated from the fraction of the dose excreted unchanged in the urine (Ae) and the AUC (CL_R = Ae/AUC). The absolute oral bioavailability (F) was obtained by comparing the AUCs after oral and intravenous administration ($F = AUC_{oral}/AUC_{intravenous}$). The maximum concentration of drug in serum (C_{max}) was defined as the highest recorded concentration and the time needed to reach C_{max} (T_{max}) was also recorded.

The statistical analysis of the data was performed using Student's t test (comparison of two means) and Student's t test for paired samples. Differences in T_{max} values were analyzed with the Wilcoxon rank test.

RESULTS

Experiment 1. A graphic plot of the average concentrations of PPA in serum and urine after intravenous infusion and oral administration of 100 mg of drug is shown in Fig. 1. At the cessation of the infusion, i.e., at 60 min, the average PPA concentration in serum was 1.23 ± 0.08 μg/ml (mean ± standard error of the mean [SEM]) whereafter it declined biexponentially with a distribution half-life of 0.17 ± 0.02 h. The other pharmacokinetic data obtained from the concentrations of drug in serum and urine are presented in Table 1. None of the subjects experienced any side effects during or after the infusion.

The degree of plasma protein binding was about 15% at drug concentrations in serum of 0.3 to 0.5 μg/ml (at 2 to 4 h) but increased to 29 to 39% at concentrations of 0.1 to 0.15 μg/ml (at 8 h).

The highest concentration of PPA in saliva was measured at 1 h, and it was 0.40 ± 0.06 and 0.23 ± 0.04 μg/ml after intravenous and oral administration, respectively. The corresponding saliva/serum concentration ratios were 0.33 and 0.32. The level in saliva decreased to 0.10 ± 0.01 and 0.12 ± 0.01 μg/ml at 2 h and then to 0.03 ± 0.01 and 0.05 ± 0.01

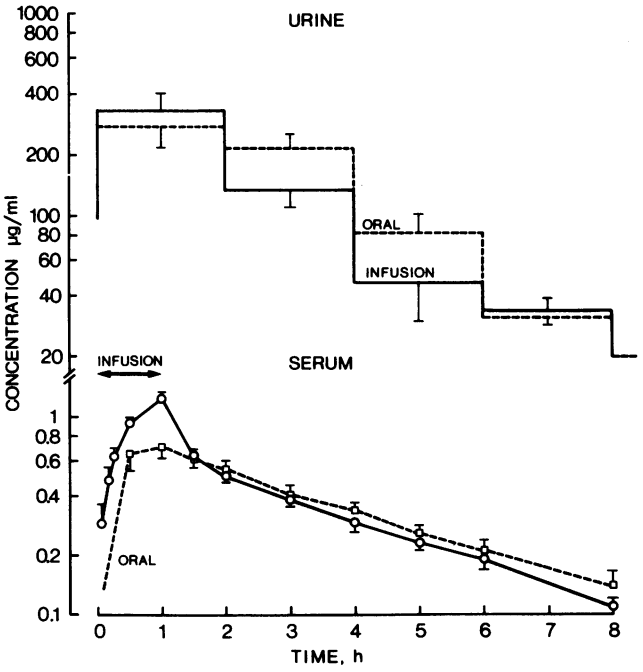

FIG. 1. Concentrations (mean ± SEM) of PPA in serum and urine after administration of a 100-mg tablet or after a 100-mg intravenous infusion to six healthy volunteers.

TABLE 1. Pharmacokinetic data (mean ± SEM) derived from concentrations of drug in serum, degree of binding to plasma proteins, and cumulative excretion of unchanged PPA in urine in six subjects after intravenous or oral doses of 100 mg each

Pharmacokinetic parameter	Intravenous infusion	Oral administration
C_{max} (μg/ml)		0.84 ± 0.07
T_{max} (h)		1.1 ± 0.3
$AUC_{0-\infty}$ (μg · h/ml)	3.7 ± 0.3	3.3 ± 0.4
Bioavailability (%)	100.0	93.1 ± 11.4
Elimination half-life (h)	3.1 ± 0.3	3.5 ± 0.6
CL_{tot} (ml/min/kg)	6.3 ± 0.5	5.6 ± 0.2
CL_R (ml/min/kg)	5.4 ± 0.6	5.0 ± 0.5
V (liters/kg)	1.7 ± 0.1	1.7 ± 0.1
Protein binding (%) at 2 h[a]	16.4 ± 5.2	13.4 ± 2.7
at 4 h[a]	16.5 ± 3.8	15.4 ± 3.6
at 8 h[a]	29.2 ± 9.5	39.1 ± 9.4
Excretion in urine (% of dose) 0–24 h	81.4 ± 4.2[b]	67.1 ± 2.8[b]

[a] The corresponding drug concentrations in serum are given in Fig. 1.
[b] Statistically significant difference ($P < 0.05$).

μg/ml at 4 h after intravenous and oral administration, respectively. At 8 h, no PPA was detectable in saliva.

Experiment 2. Graphic illustrations of the mean concentrations of PPA in serum and in urine after a single 500-mg tablet and at steady state after administration of such a tablet every 12 h are shown in Fig. 2A to C. A comparison of the drug levels in serum and urine on days 5 and 6 (Fig. 2B and C) confirmed that steady state prevailed. The pharmacokinetic data obtained from the drug concentrations in serum and urine are presented in Table 2.

At the end of a dosing interval, the average PPA concentration in urine did not go below 100 μg/ml (Fig. 2C). The chemical and the microbiological methods yielded similar concentrations of PPA in urine. The chemical method was, however, more sensitive and more accurate. In our hands, it was the only one that could be used for the determination of PPA concentrations in serum.

TABLE 2. Pharmacokinetic data (mean ± SEM) derived from concentration of PPA in serum and cumulative excretion of unchanged PPA in urine after administration of a single oral dose of 500 mg to 10 subjects and at steady state after twice-daily doses of 500 mg

Pharmacokinetic parameter	Single oral 500-mg dose	Steady-state day 6
C_{max} (μg/ml)	3.83 ± 1.0	4.27 ± 0.45
T_{max} (h)	1.4 ± 0.5	1.2 ± 0.1
C_{min} (before the morning tablet, μg/ml)		0.72 ± 0.09[a]
C_{min} (before the evening tablet, μg/ml)		0.49 ± 0.1[a]
Elimination half-life (h)	2.8 ± 0.1[b]	3.4 ± 0.2[b]
$AUC_{0-\infty}$ (μg · h/ml)	18.3 ± 1.3[c]	
AUC_{0-12} (μg · h/ml)[d]		22.1 ± 1.8[c]
CL_{tot} (ml/min/kg)	7.6 ± 0.5[c]	6.3 ± 0.5[c]
CL_R (ml/min/kg)	4.4 ± 0.2	4.3 ± 0.7
V (liters/kg)	1.9 ± 0.2	1.9 ± 0.2
Excretion in urine (% of dose)		
0–12 h	53.6 ± 3.2	57.0 ± 3.1
0–24 h	58.0 ± 2.6	61.2 ± 3.5
0–72 h	58.9 ± 3.0	63.7 ± 5.1

[a] Statistically significant difference ($P < 0.001$).
[b] Statistically significant difference ($P < 0.01$).
[c] Statistically significant difference ($P < 0.05$).
[d] AUC_{0-12}, AUC of a dosage interval at steady state.
[e] Statistically significant difference ($P < 0.05$).

DISCUSSION

The bioavailability of 100-mg PPA doses averaged 93%, as estimated from the AUCs obtained after oral and intravenous administration. The bioavailability calculated from the urinary recoveries (Table 1) was 82%, which is in good agreement with the ratio of the renal clearance to the total

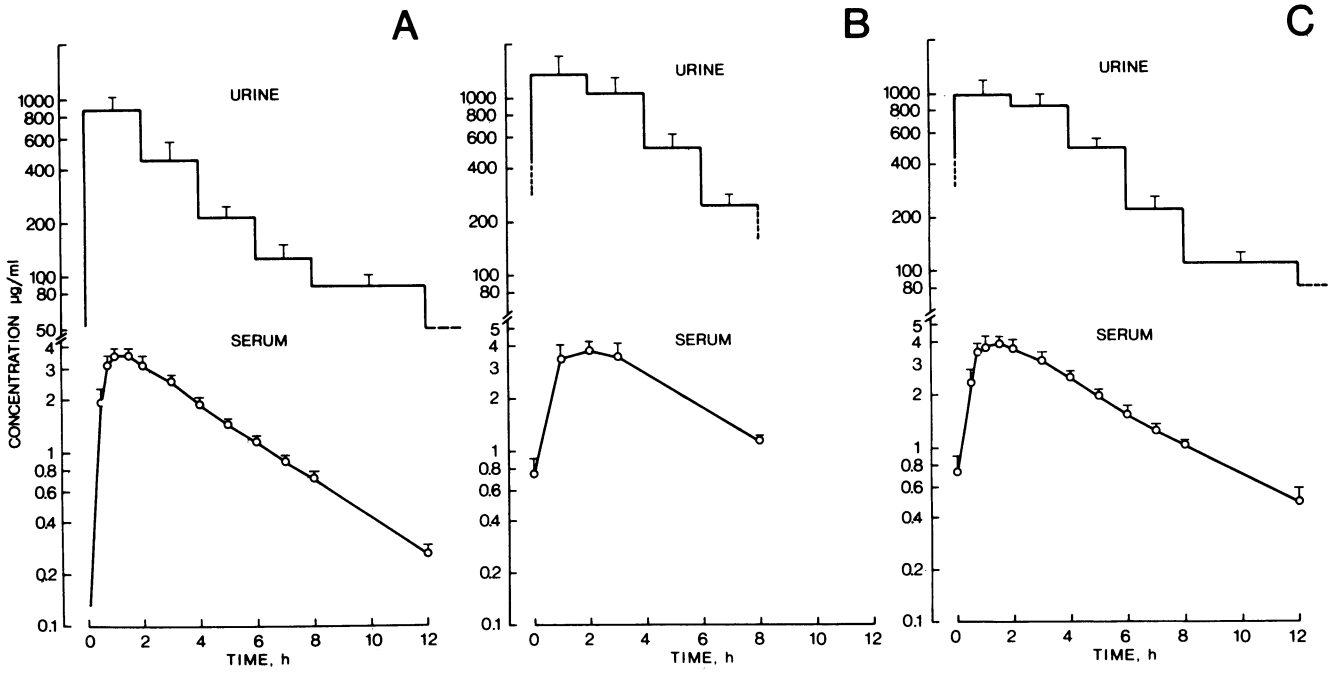

FIG. 2. Concentrations (mean ± SEM) of PPA in serum and urine. (A) After administration of a single 500-mg tablet to 10 healthy volunteers. (B) On day 5 of twice-daily administration of a 500-mg tablet to the same subjects as in (A). The only reason for sampling on this day was to confirm that steady state prevailed. (C) On day 6 at steady state, after twice-daily administration of a 500-mg tablet.

clearance. After ingestion of a 100-mg and a 500-mg tablet, the maximum concentrations of drug in serum, as well as the amounts absorbed, were proportional to the dose (Tables 1 and 2). There were, however, marked interindividual differences both in the rate and in the extent of bioavailability, the differences in rate being greater.

The maximum concentration of PPA in serum at steady state predicted from the data obtained after the single dose (14) of 500 mg was 4.2 μg/ml. This conforms with the value measured (Table 2), suggesting that, upon multiple dosing, little or no accumulation took place. Support to this view is given by the fact that the accumulation index (19) was only 0.41. The minimum concentration of PPA in serum preceding ingestion of the morning tablet was always higher than that preceding ingestion of the evening tablet. This phenomenon may mainly be due to the basic physiological fact that cardiac output is smaller during the night than during the day.

Previous studies have shown that the binding of PPA to plasma proteins is low in normal subjects (16) and still lower in uremic patients (12). The present results confirm a low degree of binding and suggest that the binding is saturable even at low concentrations (Table 1 and Fig. 1). When therapeutic doses of PPA are used, clinically important pharmacokinetic interactions due to displacement from plasma proteins are almost excluded. With NA, however, there is a theoretical basis for the occurrence of such interactions, because NA is highly bound to plasma proteins (9, 10).

After cessation of the intravenous infusion, the concentration of PPA in serum declined biexponentially, whereas no separate distribution phase could be distinguished after oral administration (Fig. 1 and 2); this indicates that the disposition of PPA, intravenously and orally, may be satisfactorily described as two- and one-compartment open models, respectively. Infusion experiments performed by others (8) have led to the same conclusion.

The slightly different distribution volumes obtained after administration of 100 or 500 mg may be due to interindividual variations, but they may also in part be explained by a saturable binding to plasma proteins. These apparent distribution volumes are in agreement with the fairly good penetration characteristics of PPA observed in *Macaca mulatta* and beagle dogs (16). In the monkeys, however, PPA did not penetrate the blood-brain barrier, despite twice-daily treatment for 1 month with 50-mg/kg doses (16). It is conceivable that PPA does not easily enter the central nervous systems of humans either, and this could explain why it more rarely causes neurological disturbances than other quinolones used as urinary antiseptics (5). On the other hand, therapeutic concentrations of PPA have been attained in prostate glands (1).

The mean elimination half-life was 3.1 h, which exceeds the value obtained in another study in which PPA was quantitated by a spectrophotofluorimetric technique (2). The elimination was mainly renal, and the renal clearance exceeded the glomerular filtration rate by about three times, indicating considerable tubular secretion. The present results suggest that with increasing concentrations of drug in serum, the extrarenal clearance, probably mainly hepatic, became more important, but it cannot be established whether this was associated with a saturation of the active renal process. This assumption is supported by the fact that in normal subjects the fraction of PPA recovered in feces increases with the dose (3, 16). There were marked differences between the elimination half-lives as well as between the clearance values achieved in the present experiments. It is not known to what extent these differences reflect inter- and intraindividual variability. Neither is it known how renal clearance is affected by the acidity of urine or how hepatic clearance is affected by local blood flow.

PPA is metabolized to but a small extent in humans, metabolites in urine accounting for less than 6% of the renally excreted parent compound (4, 7); NA on the other hand is metabolized extensively (4, 6). Therefore, agents altering drug metabolism are more likely to interfere with the metabolism of NA than with that of PPA. The excretion of PPA in saliva was so low that its pharmacokinetic significance remains open even though there may be a constant saliva/serum ratio.

In conclusion, the pharmacokinetics of PPA, as observed at the use of a recommended dosage regimen in healthy subjects, may be characterized by rapid absorption, low binding to plasma proteins, low degree of biotransformation, and high and mainly renal clearance maintaining throughout the dosing interval a concentration of the parent compound in urine which by 5 to 20 times exceeds its MICs against several bacteria commonly causing infections of the urinary tract (13, 17).

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